REMARKS

By the present amendment, Applicants amend claims 17, 21, and 26-29 and add claims 31-33. The specification fully supports these amendments, which do not add prohibited new matter. The Office will find support for these amendments throughout the specification.

Claim Rejections – 35 U.S.C. § 112, First Paragraph

The Office Action rejects claims 17-30 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enabling support in the specification. The Action asserts that the specification, while providing enabling support for therapeutic treatment of melanoma by administration of compound 50, does not reasonably provide enablement for preventative or therapeutic treatment of dermal pigmentation and/or skin cancer. Applicants respectfully disagree.

With regard to the preventative or therapeutic treatment of dermal pigmentation, Applicants respectfully direct the Office's attention to the first paragraph of the Background section of the present application.

> Ultraviolet irradiation to skin causes burn-like damage to skin, and also induces hypodermic pigmentation to darken the skin. This phenomenon is well known as sunburn; however, a mechanism of the hypodermic pigmentation has not been clearly revealed until a recent date. When the skin is exposed to ultraviolet light, cytokines such as TNF(tumor necrosis factor), IL-1(interleukin-1), and bFGF (basic fibroblast growth factor) are secreted upon the stimulation, and then transformation and proliferation of melanocytes occur due to the stimulation, which are melanin production cells, to produce a large amount of melanin pigment, and successively the pigment moves to epidermal keratinocytes and deposits to darken the skin (American Journal of Pathology, Vol.158, No.3, p.943-953, 2001).

This section of the specification clearly explains how ultraviolet light induces secretion of TNF, IL-1, and bFGF, which result in the transformation and proliferation of melanocytes. This then results in the overproduction of dermal pigment, which moves to epidermal keratinocytes, thereby darkening the skin. In view of this cascade of events, Applicants respectfully submit that compounds that inhibit the transformation and proliferation of melanocytes would be expected to prevent dermal pigmentation by the same pathway.

Applicants also note that the rejection is at least partly based upon the Office's interpretation of the word "prevention," which the Office indicates means "'to keep from happening or existing,' i.e., to completely eradicate." (Office Action, paragraph spanning pages 5-6.) Applicants respectfully submit that this definition is overly limiting, and inconsistent with the art. Initially, Applicants submit that "to keep from happening or existing" does not necessarily imply that the effect is complete, as the Office suggests. Applicants submit that something can be kept from happening or existing at a level of less than complete – and indeed, can be prevented from occurring at an infinite number of levels.

Applicants also submit that requiring complete eradication is inconsistent with the art's use of the term "prevention." Wikipedia's entry for "sunscreen," for example, states that "[m]edical organizations such as the American Cancer Society recommend the use of sunscreen because it *prevents* the squamous cell carcinoma and the basal cell carcinoma." (Wikipedia: Sunscreen.) Indeed, the American Cancer Society has an entire section on its website entitled, "Skin Cancer *Prevention* and Early Detection," in which it advises applying sunscreen to reduce the effects of ultraviolet light on the skin. (A copy of the section is attached hereto.) Applicants respectfully submit that these are simply a couple of the many examples in which "prevention" is used in this art to mean "reducing the likelihood of," which is how Applicants' have used the term in the specification and claims.

Applicants also respectfully note that the claims under consideration are not directed to an unlimited number of compounds, and indeed, are limited to compounds that are reasonably expected by the inventors to have actions similar to those of compound 50. Applicants have described numerous specific examples falling within the scope of the present claims and have stated that such compounds are expected to be useful in the manners recited in the present claims. Nothing more is required of Applicants to enable the practice of the present invention. The burden is on the Office to establish why compounds falling within the scope of Applicants' claims would be expected *not* to function as Applicants have suggested they will. The Office has failed to present such evidence.

Indeed, the only evidence put forth by the Office to rebut Applicants' assertions regarding enablement pertains to the recitation of "skin cancer" in Applicants' claims. The Office asserts

that Brown et al., Lancet Oncology, 2004, 5, 497-508, establishes that a non-surgical therapy that is effective against one form of skin cancer – actinic keratinosis – will not predictably be effective against another form – melanoma. However, Applicants respectfully submit that the Office appears to have misinterpreted the discussion in Brown et al. Brown et al. specifically states that "[u]se of [photodynamic therapy] for melanoma has not yet been pursued substantially in any study because of the difficulty in achieving good penetration of light through pigmented lesions, and partly because of ethical considerations about the aggressive nature of the disease." (Brown et al. at 500, right column, first paragraph.) Applicants submit that this passage stands only for the proposition that photodynamic therapy had not been successfully used in melanoma up to 2004 because of practical and ethical concerns.[1] Applicants submit that this passage does not provide support for the Office's position that Applicants' working example in melanoma cannot be extended to other skin cancer forms.

The Office also cites to a web page that discusses melanoma, but it is not clear from the record why the Office refers to this publication. The web page discusses melanoma in some detail, but the Office fails to explain how it pertains to the rejection, and in particular, how it supports the Office's conclusion that Applicants' specification fails to enable treatment of other forms of skin cancer.

In conclusion, Applicants respectfully submit that the claims fully satisfy the requirements of 35 U.S.C. § 112, first paragraph, and respectfully request withdrawal of the rejection.

Claim Rejections – 35 U.S.C. § 102

The Office Action rejects claims 17-30 under 35 U.S.C. § 102(b) as allegedly anticipated by U.S. Patent No. 3,332,996, to Zerweck et al. ("the '996 patent"). The Action asserts that the '996 patent discloses compound 50 and its administration to skin, and thus, the results disclosed in the specification would be an inherent result of the administration. Applicants respectfully disagree with the rejection.

---

1 Applicants attach hereto a publication from 2008 (Fasanella et al., *Gastrointestinal Endoscopy* 2008 (in press)) describing the successful treatment of duodenal metastatic melanoma with photodynamic therapy. The article also notes that photodynamic therapy has been successfully used to treat cutaneous metastatic melanoma lesions.

Applicants agree that the '996 patent discloses compound 50. However, Applicants disagree that the '996 patent discloses its administration to skin in a manner that would anticipate the present invention. The relevant section of the '996 patent states:

> The salicylanilides according to our invention containing at least two trifluoromethyl groups are excellent disinfectants, especially when used for sanitation purposes. They may be employed as such in the control of bacterial infectious diseases of the skin, or when incorporated into the conventional washing agents, detergents and cosmetics, they may also be employed in the disinfectant cleaning of objects of all kinds, such as textile materials, apparatus, equipment and containers in the beverage industry, milk cans, etc.

('996 patent, column 2, lines 14-23.)

Applicants' claims are directed to methods "for preventive and/or therapeutic treatment of dermal pigmentation and/or skin cancer in a mammal including a human, which comprises the step of administering *a preventively and/or therapeutically effective amount*" of the compound. Applicants respectfully submit that the '996 patent's disclosure fails to teach or suggest the administration of a *preventively and/or therapeutically effective amount*. That is, there is nothing in the disclosure that suggests what amount should be administered, let alone a *preventively and/or therapeutically effective amount* for the presently claimed indications. Applicants respectfully submit that the '996 patent does not anticipate the presently claimed invention.

While Applicants respectfully submit that the Office has failed to carry its burden in establishing anticipation of the presently claimed invention, Applicants provide herewith additional evidence that suggests that the disclosure of the '996 patent would not inherently anticipate the presently claimed invention. In order to determine whether or not compound 50 of the present invention exhibits cytotoxic activity against primary normal human cutaneous keratinocytes (Cell System Kc Cells; Cat. CS2KO101; DS Pharma Biomedical Co., Ltd.), experiments were conducted according to the Organization for Economic Cooperation and Development (OECD) Guideline for the Testing of Chemicals, No. 473. Results obtained are summarized below.

Final Concentration of Compound 50 (μg/mL)	The relative rate of proliferation (%)	
	S9(-)	S9(+)
0	100	100
0.75	91.6	98.6
3.0	96.0	111.3

From these results, it was concluded that the inhibitory action of compound 50 against the transformation and proliferation of melanocytes is not toxic action, and the inhibitory action by compound 50 is specific to particular kind of cells. Further, structures of mammalian cells are different from those of bacterial cells, and therefore, one of ordinary skill in the art would not have considered that the mechanism of action of compound 50 against bacteria (as in the '996 patent) is substantially the same as the action of compound 50 against melanocytes.

In conclusion, Applicants respectfully submit that the '996 patent fails to disclose Applicants' claimed invention, and respectfully request withdrawal of the rejection under 35 U.S.C. § 102(b).

CONCLUSION

If there are any comments or questions, the undersigned may be contacted at the below-listed telephone number.

Respectfully submitted,
Akiko ITAI et al

Bruce H. Bernstein
Reg. No. 29,027 42,920

September 8, 2008
GREENBLUM & BERNSTEIN, P.L.C.
1950 Roland Clarke Place
Reston, VA 20191
(703) 716-1191